Time dependent multivariate distributions for piecewise-deterministic models of gene networks

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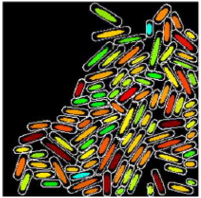
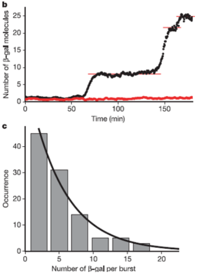
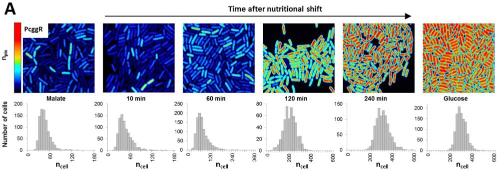
Stochastic gene expression



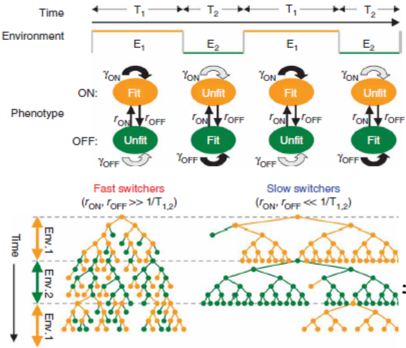
Heterogeneity of clone cells populations

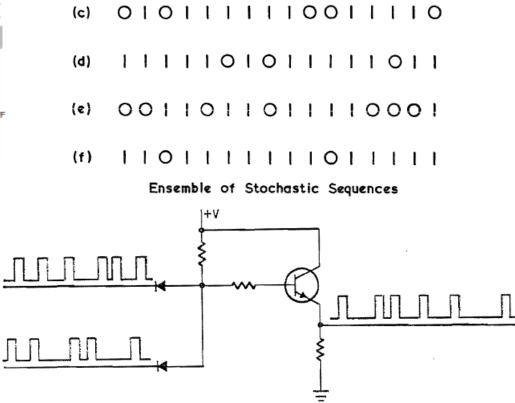


Dynamics, individual cell



Dynamics of stochastic gene expression, population



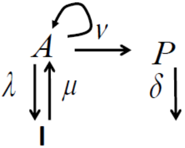


Adaptation of heterogeneous populations: stochastic switching

Gaines/Poppelbaum stochastic computing

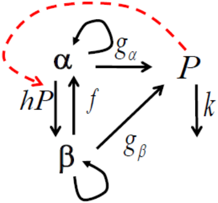
Markovian models of stochastic promoters

Peccoud, Ycart (1995)



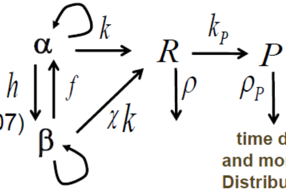
time dependence of moments and of distribution
Hypergeometric fonctions to compute steady state distribution

Hornos et al (2005)
Ramos et al (2011)



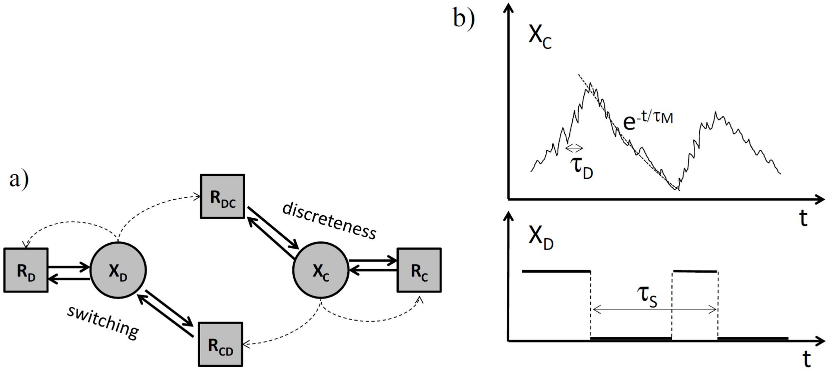
steady state distribution
time dependent distribution
Kummer functions
Heun function

Innocentini and Hornos (2007)



time dependence of distribution and moments.
Distributions by recurrences

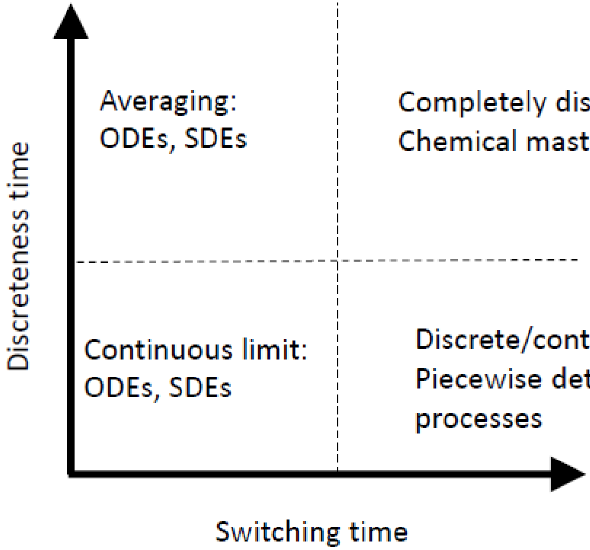
Multi-scaleness of stochastic gene expression



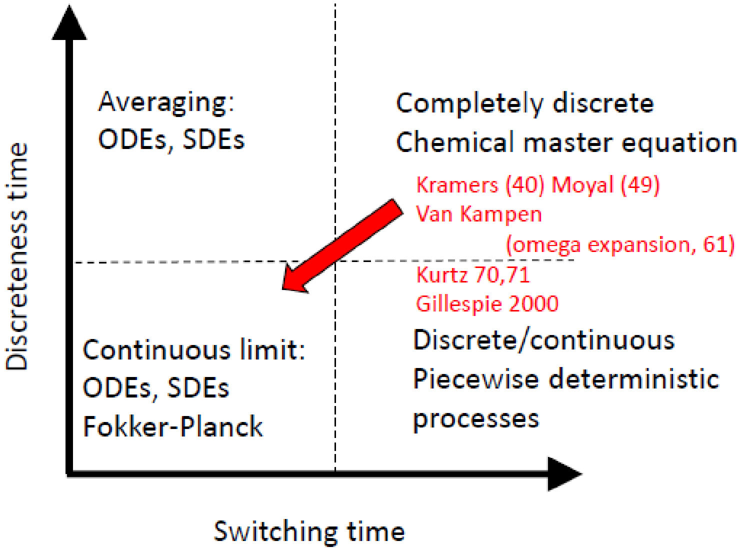
Switching and discreteness timescales (a) The partition of species and of the reactions; dotted lines mean that reaction rates depend on the corresponding species. (b) Typical trajectories of continuous and discrete variables: switched processes.

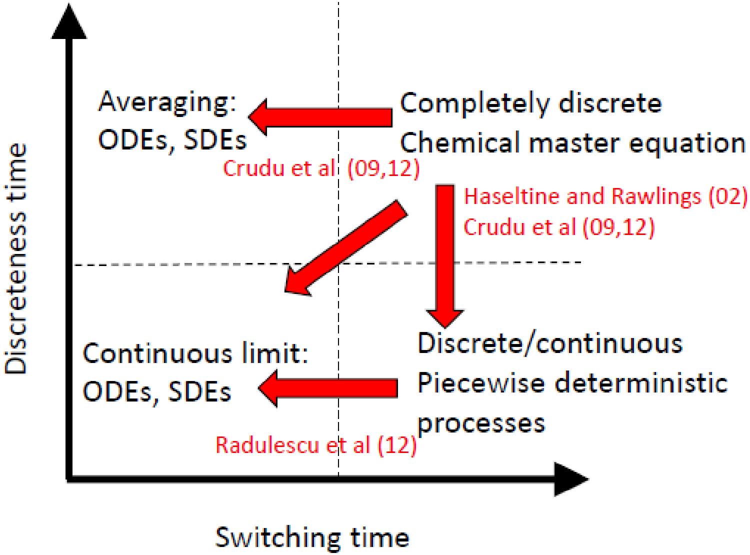
Radulescu et al Phys.Rev.E 85 (2012) 041919.

Continuous and hybrid approximations



Continuous and hybrid approximations




Discreteness time
Averaging:
ODEs, SDEs
Completely discrete
Chemical master equation
Crudu et al (09,12)
Haseltine and Rawlings (02)
Crudu et al (09,12)
Continuous limit:
ODEs, SDEs
Discrete/continuous
Piecewise deterministic
processes
Radulescu et al (12)
Switching time

Partial omega expansion

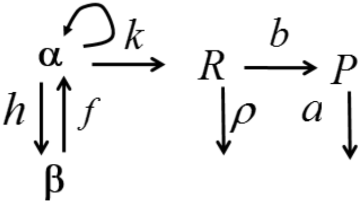
Ω: size variable, $x_c = X_c/\Omega$.

$$\begin{aligned}
\frac{\partial p}{\partial t}(X_D, x_c, X, t) &= \sum_{i \in \mathscr{R}_D \cup \mathscr{R}_{DC}} [V_i(X_D - \gamma_i^D, x_c; \mu) p(X_D - \gamma_i^D, x_c, t) - V_i(X; \mu) p(X_D, x_c, t)] + \\
&+ \sum_{i \in \mathscr{R}_C \cup \mathscr{R}_{CD}} \Omega [v_i(X_D, x_c - \gamma_i^C/\Omega; \mu) p(X_D, x_c - \gamma_i^C/\Omega, t) - v_i(X; \mu) p(X_D, x_c, t)]
\end{aligned}$$

Master equation

$$\begin{aligned}
\frac{\partial p}{\partial t}(X_D, x_c, t) &= -\frac{\partial[\Phi(X_D, x_c; \mu) p(X_D, x_c, t)]}{\partial x_c} + \sum_{i \in \mathscr{R}_D \cup \mathscr{R}_{DC}} [V_i(X_D - \gamma_i^D, x_c; \mu) p(X_D - \gamma_i^D, x_c, t) - \\
&- V_i(X_D, x_c; \mu) p(X_D, x_c, t)], \text{where} \\
\Phi(X_D, x_c; \mu) &= \sum_{i \in \mathscr{R}_C \cup \mathscr{R}_{CD}} \gamma_i^C v_i(X_D, x_c; \mu)
\end{aligned}$$

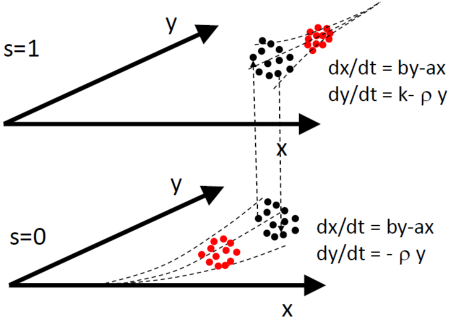
Liouville-master equation



$X : P,\ Y : R.$

$$
\begin{aligned}
\frac{\partial p}{\partial t}(1,X,Y,t) &= k\Omega(p(1,X,Y-1,t) - p(1,X,Y,t)) + \\
&+ \rho((Y+1)p(1,X,Y+1,t) - Yp(1,X,Y,t)) + bY(p(1,X-1,Y,t) - p(1,X,Y,t)) + \\
&+ a((X+1)p(1,X+1,Y,t) - Xp(1,X,Y,t)) + fp(0,X,Y,t) - hp(1,X,Y,t) \\
\frac{\partial p}{\partial t}(0,X,Y,t) &= \rho((Y+1)p(0,X,Y+1,t) - Yp(0,X,Y,t)) + bY(p(0,X-1,Y,t) - p(0,X,Y,t)) + \\
&+ a((X+1)p(0,X+1,Y,t) - Xp(0,X,Y,t)) + hp(1,X,Y,t) - fp(0,X,Y,t)
\end{aligned}
$$

Single gene ON/OFF promoter: Liouville-master equation



$$\frac{\partial p}{\partial t}(1,x,t) = -\frac{\partial[(by-ax)p(1,x,y,t)]}{\partial x} - \frac{\partial[(k-\rho y)p(1,x,y,t)]}{\partial y} + fp(0,x,y,t) - hp(1,x,y,t)$$

$$\frac{\partial p}{\partial t}(0,x,y,t) = -\frac{\partial[(by-ax)p(0,x,y,t)]}{\partial x} - \frac{\partial[-\rho y p(0,x,y,t)]}{\partial y} + hp(1,x,y,t) - fp(0,x,y,t)$$

$x : X/\Omega$, $y : Y/\Omega$.

Single gene ON/OFF promoter: Monte-Carlo

(1) Set $s = s^{(0)}$, $x = x^{(0)}$, $y = y^{(0)}$, $t = t_0$, $i = 0$.

(2) Generate $u \sim \mathscr{U}[0,1]$,

(3) Integrate the system of ODEs

$$\begin{cases} \frac{dx}{dt} = by - ax \\ \frac{dy}{dt} = k\delta_{s,1} - \rho y, \\ \frac{dF}{dt} = -(f+h)F, \\ x(t_i) = x^{(i)}, y(t_i) = y^{(i)}, F(t_i) = 1, \end{cases}$$

between t_i and $t_i + \tau_i$ with the stopping condition $F(t_i + \tau_i) = u$.

(4) Generate $v \sim \mathscr{U}[0,1]$ use it to pick $s^{(i+1)}$. (the decision is made in the same way as in the Gillespie algorithm).

(5) Change the system state $(s^{(i)}, x, y)$ to $(s^{(i+1)}, x, y)$, and the time t_i to $t_{i+1} = t_i + \tau_i$.

(6) Reiterate the system from 2) with the new state until a time $t_{\max}$ previously defined is reached.

Single gene ON/OFF promoter: push forward

(1) Consider fixed partition $t_0 = 0, t_1, \ldots, t_N = T$ fine enough such that s is constant on most subintervals.

(2) For each possible instance $s_0, s_1, \ldots, s_{N-1}$ compute its probability

$$\mathbb{P}[s_0, \ldots, s_{N-1}] = \sum_{s_0, \ldots, s_{N-1}} \mathbb{P}[s_0]\,\mathbb{P}[s_1|s_0]\ldots\mathbb{P}[s_{N-1}|s_{N-2}]$$

where $\mathbb{P}[s_{k+1}|s_k]$ is the exact solution of
$\frac{dp_0}{dt} = -fp_0 + h(1-p_0), \quad p_1 = 1 - p_0.$

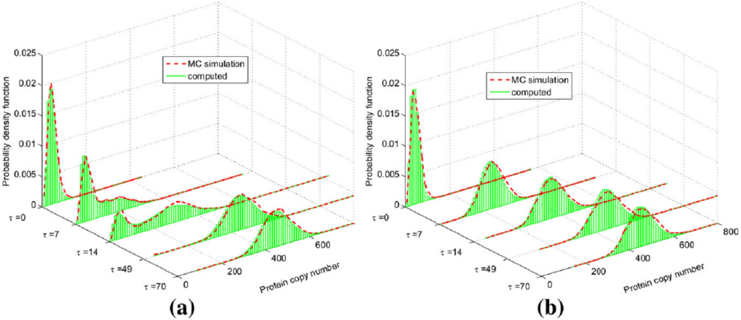
(3) Compute $x(t)$ and $y(t)$ as exact solutions of
$\frac{dx}{dt} = by - ax, \quad \frac{dy}{dt} = k\delta_{s,1} - \rho y$

(4) Gather all $x(t), y(t)$ leading to the same distribution bin in (x, y) plane and sum the probabilities.

NB: we use the exact distribution of s to obtain the one of x, y. Possible to use the exact distribution of (s, y) to obtain the one of x

Innocentini et al, Bull Math Biol (2016) 78:110-131.

Single gene ON/OFF promoter: illustration of the methods



Dynamical evolution of protein probability density for slow switch ($\varepsilon = (h+f)/\rho = 0.1$) in a) and fast switch ($\varepsilon = 5$) in b).

Innocentini et al, Bull Math Biol (2016) 78:110-131.

- The methods can be applied to any combination of promoters with or without feed-back.
- Limitations imposed by the number of distinct genes N_g.
- Push-forward is better than solving the 2^{N_g} Liouville-master PDEs.
- Push-forward is better than Monte-Carlo for small to medium N_g (circuits).